VIP Annulated Rings

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Catalytic Enantioselective Synthesis of Chiral Tetraphenylenes: Consecutive Inter- and Intramolecular Cycloadditions of Two Triynes**

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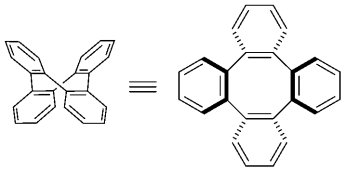
Tetraphenylene is a structurally unique saddle-shaped molecule, wherein four benzene rings are *ortho* annulated to construct an eight-membered ring system, in which the benzene rings are arranged upward and downward (Scheme 1).[1] Tetraphenylene has D_{2d} point symmetry and



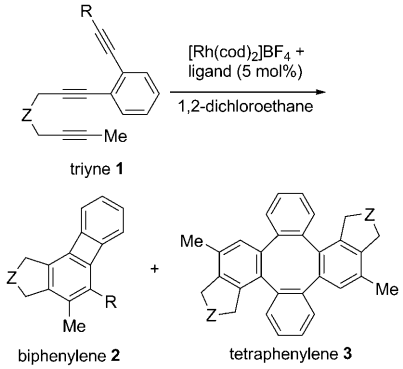
Scheme 1. Structure of tetraphenylene.

is not chiral; however, substitution on the benzene rings could induce a chiral π-conjugated system because of a high barrier to inversion.[2] Therefore, substituted tetraphenylenes are promising candidates as chiral functional molecules having configurational stability.[3] However, there are only two major approaches to the construction of the tetraphenylene skeleton, both first reported over 20 years ago:[4] 1) homocoupling of 2,2′-dimetalbiphenyl, which is prepared by metalation of 2,2′-dihalobiphenyl[5] or metal-mediated C–C bond cleavage of biphenylene,[6] and 2) Diels–Alder reaction of 1,2,5,6-dibenzocycloocta-3,7-diyne, which has two strained alkyne moieties, with furan and subsequent reductive aromatization.[7] For the synthesis of chiral tetraphenylene derivatives, resolution of the racemic compounds is a reliable protocol. To this end, Wong and co-workers have comprehensively studied the asymmetric synthesis and the use of chiral poly(hydroxy)tetraphenylenes.[8] The only example of an enantioselective synthesis is the sparteine-mediated lithiation of 2,2′-dibromobiphenyl derivatives and subsequent coupling using an excess amount of $CuBr_2$, for which moderate enantioselectivity was achieved.[9]

Herein we disclose a new [2+2+2] cycloaddition-based strategy for the synthesis of substituted tetraphenylenes, and its application to asymmetric synthesis.

We recently reported the iridium-catalyzed enantioselective formal [4+2] cycloaddition of biphenylenes with alkynes.[10] During the course of this study, to prepare various functionalized biphenylenes, we examined the [2+2+2] cycloaddition of phenylene-bridged 1,6,10-triyne **1aa**;[11] the desired biphenylene **2aa** was obtained in high yield in the presence of a cationic Rh–*rac*-binap catalyst[12] (Table 1, entry 1). When triyne **1ab**, having a terminal alkyne moiety, was submitted using the same catalyst, a symmetrical dimer of triyne **1ab** was obtained as a major product (Table 1, entry 2). We varied the bidentate phosphine ligand on the catalyst and found that biphep resulted in selective formation of the dimer (Table 1, entry 3). Various kinds of NMR analyses supported

Table 1: Rhodium-catalyzed reaction of several triynes for the synthesis of biphenylenes and tetraphenylenes.



Entry[a]	R, Z	Triyne	*T* [°C]	*t* [h]	Yield of **2** [%]	Yield of **3** [%]
1	Bu, NTs	**1aa**	40	2	89 (**2aa**)	–
2	H, NTs	**1ab**	RT	1	20 (**2ab**)	37 (**3ab**)
3	H, NTs	**1ab**	RT	2	–	72 (**3ab**)
4	H, $C(CO_2Me)_2$	**1bb**	60	2	–	92 (**3bb**)
5[b]	H, O	**1cb**	RT	4	–	93 (**3cb**)

[a] Ligand: *rac*-binap for entries 1 and 2, biphep for entries 3-5. [b] 10 mol% catalyst was used. Ts = 4-toluenesulfonyl, cod = 1,5-cyclooctadiene, binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, biphep = (2,2′-bis(diphenylphosphino)-1,1′-biphenyl).

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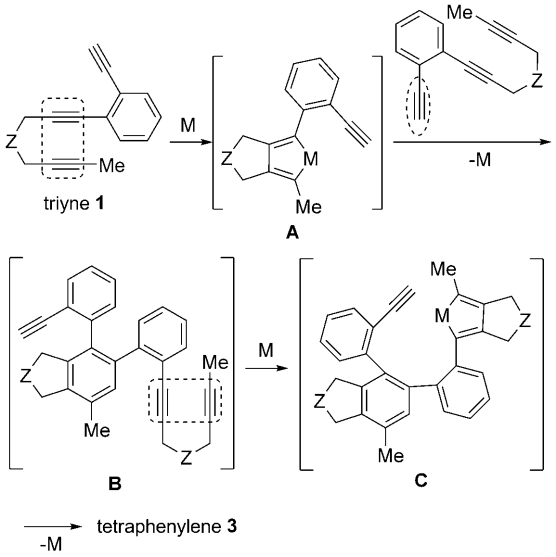
the tetraphenylene skeleton, and we finally determined the structure of cycloadduct **3ab** by X-ray diffraction analysis (the ORTEP diagram is depicted in the Supporting Information). The carbon- and oxygen-tethered triynes **1bb** and **1cb** were also transformed into the corresponding tetraphenylenes **3bb** and **3cb** in high yield using the same catalyst (Table 1, entries 4 and 5).

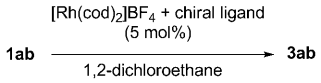
We considered a plausible mechanism for the above-mentioned reaction, which includes consecutive inter- and intramolecular cycloadditions (Scheme 2). Oxidative coupling of the 1,6-diyne moiety of the first triyne gave metallacyclopentadiene **A**. Chemo- and regioselective intermolecular coupling with terminal alkyne moiety of the second triyne gave primary cycloadduct **B**. Oxidative coupling of 1,6-diyne moiety of the second triyne and intramolecular coupling with the remaining terminal alkyne moiety of the first triyne gave tetraphenylene **3**.[13] Thus, the present protocol provides a new and concise approach to substituted tetraphenylenes. We additionally investigated enantioselective variants of the present reaction.



Scheme 2. Plausible mechanism of dimerization of triyne **1**.

Using nitrogen-tethered triyne **1ab** as a model substrate, we examined several chiral phosphine ligands (Table 2). Chiral biphep derivatives definitely induced enantioselectivity but with poor *ee* values (Table 2, entries 1 and 2). Binap itself was ineffective (Table 2, entry 3) but Cy-binap was the ligand of choice after thorough screening (Table 2, entry 4). Among ligands other than binap derivatives, duphos ligands proved effective, and good *ee* values were achieved by using Et-duphos under reflux conditions in 1,2-dichloroethane (Table 2, entries 6 and 7). Finally, QuinoxP*[14] induced the best enantioselectivity and both enantiomers were obtained using (*R*,*R*)- and (*S*,*S*)-ligands, respectively (Table 2, entries 8 and 9).[15,16] Using 2 mol% of the catalyst achieved the same results, but a longer reaction time was required (Table 2, entry 10).

Table 2: Screening of chiral ligands for enantioselective reaction.



Entry	Ligand	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]
1	(*R*)-MeO-biphep	RT	2	88	14
2	(*R*)-Cl-MeO-biphep	RT	2	80	15
3	(*S*)-binap	RT	1	45	−15
4	(*R*)-Cy-binap	RT–60	5	84	79
5	(+)-Cy-segphos	RT–60	5	83	57
6	(*S*,*S*)-Me-duphos	reflux	6	97	−48
7	(*S*,*S*)-Et-duphos	reflux	3	57	−76
8	(*R*,*R*)-QuinoxP*	reflux	6	65	88
9	(*S*,*S*)-QuinoxP*	reflux	6	65	−87
10[a]	(*R*,*R*)-QuinoxP*	reflux	24	65	87

[a] 2 mol% chiral catalyst was used. MeO-biphep = 6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl, Cl-MeO-biphep = 5,5′-dichloro-6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl, Cy-segphos = 5,5′-Bis(dicyclohexylphosphino)-4,4′-bi-1,3-benzodioxole, Me-duphos = 1,2-bis(2,5-dimethylphospholano)benzene, Et-duphos = 1,2-bis(2,5-diethylphospholano)benzene, QuinoxP* = 2,3-bis(*tert*-butyl-methylphosphino)quinoxaline.

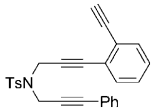
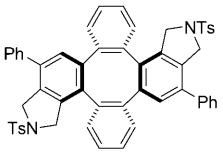
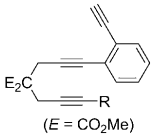
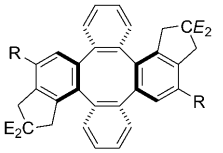
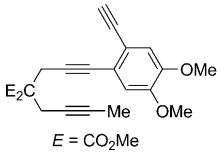
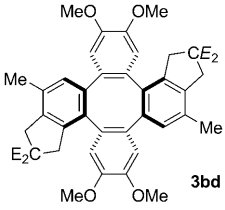
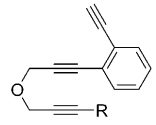
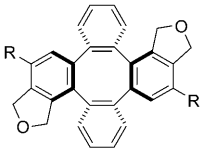
By using either the Rh–Cy-binap or Rh–QuinoxP* catalyst, we investigated the reaction of several triynes (Table 3). For the phenyl-substituted triyne **1ac**, the reaction using the Cy-binap induced far better results than did the QuinoxP* catalyst, with *ee* values of more than 90% (Table 3, entries 1 and 2). For carbon-tethered triynes **1bb** and **1bc** having methyl and phenyl groups, respectively, on their alkyne termini, the reaction with the Cy-binap catalyst yielded the corresponding tetraphenylenes **3bb** and **3bc** with excellent *ee* values (Table 3, entries 3–5). The methoxy group on the benzene ring was tolerable, and the tetramethoxy tetraphenylene **3bd** was prepared from the dimethoxy triyne **1bd** (Table 3, entry 6). Oxygen-tethered triynes **1cb** and **1cc** were also good substrates but the *ee* values of the products were lower than those of their carbon-tethered counterparts (Table 3, entries 7–9). However, when a 4-bromophenyl group was introduced, almost perfect enantioselectivity was achieved by using the Cy-binap catalyst (Table 3, entry 10). These results indicate that Cy-binap is a generally good chiral ligand, and QuinoxP* is well suited for use with methyl-substituted triynes.

In summary, we realized the dimerization of triynes, possessing phenylene-bridged 1,5-diyne moiety, by consecutive inter- and intramolecular cycloadditions. It provides a new way to access substituted tetraphenylene derivatives. By using chiral rhodium catalysts, the first catalytic and highly enantioselective synthesis of chiral tetraphenylenes was achieved. Evaluations of chemical and physical properties of the chiral tetraphenylenes and their use as a new family of functional molecules are in progress.

Experimental Section

Typical experimental procedure (Table 3): $[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) and Cy-binap or QuinoxP* (0.005 mmol) were placed in a Schlenk tube, which was then evacuated and backfilled with argon

Table 3: Substrate scope for the synthesis of chiral tetraphenylenes.

Entry	Triyne	Ligand	*T* [°C]	*t* [h]	Tetraphenylene	Yield [%][a]	*ee* [%][b]
							
1	**1 ac**	Cy-binap	reflux	24	**3 ac**	62	95
2		QuinoxP*	reflux	6		trace	–
							
3	**1 bb** (R = Me)	Cy-binap	60	24	**3 bb** (R = Me)	86	97
4	**1 bb** (R = Me)	QuinoxP*	60	24	**3 bb** (R = Me)	50	79
5	**1 bc** (R = Ph)	Cy-binap	60	24	**3 bc** (R = Ph)	45	96
							
6	**1 bd**	Cy-binap	60	24	**3 bd**	64	82
							
7	**1 cb** (R = Me)	Cy-binap	RT–60	5	**3 cb** (R = Me)	80	75
8	**1 cb** (R = Me)	QuinoxP*	RT–60	5	**3 cb** (R = Me)	59	83
9	**1 cc** (R = Ph)	Cy-binap	RT–reflux	6	**3 cc** (R = Ph)	56	85
10	**1 cd** (R = 4-BrC_6H_4)	Cy-binap	60	1	**3 cd** (R = 4-BrC_6H_4)	56	>99

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase using Daicel Chiralpak IC or IA (see the Supporting Information).

(three times). Dichloromethane (1.0 mL) was added to the reaction vessel, which was then filled with hydrogen. The reaction mixture was then stirred at ambient temperature for 30 min under the hydrogen atmosphere. After removal of the solvent and hydrogen under reduced pressure, the reaction vessel was filled with argon. 1,2-Dichloroethane (0.1 mL) was added to the flask and the mixture was stirred, giving a red solution. Then, a 1,2-dichloroethane solution (0.4 mL) of triyne (0.05 mmol) was added to the red solution and then the mixture was stirred at the appropriate temperature (see Table 3). After the completion of the reaction, the volatiles were removed under reduced pressure, and the crude mixture was purified by preparative thin-layer chromatography to give a chiral tetraphenylene. The enantiomeric excess was determined by HPLC analysis using a chiral column.

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[13] The reaction of biphenylene **2ab** using Rh–biphep catalyst did not give tetraphenylene **3ab** at all. This result clearly denies the homo-coupling mechanism of biphenylene for the present transformation.
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[15] The reaction conditions were investigated on a 0.05 mmol scale, but the reaction using Rh–QuinoxP* catalyst certainly proceeded with the almost same yield and *ee* value (68%, 88% *ee*) on a 0.5 mmol scale.
[16] The absolute configuration of product **3ab** was determined by the circular dichroism exciton chirality method (see the Supporting Information), but the final determination was deferred to a future publication.

